

TORISEL[®] (temsirolimus) Reimbursement and Billing Guide



**Please see Important
Safety Information on pages 3 and 4
and accompanying Prescribing Information.**

Disclaimer - The information contained in this guide is provided for educational purposes only. It is intended to assist providers in understanding the reimbursement process when delivering health care services. We strongly suggest that you consult your local payer organization with regard to specific reimbursement policies. The information contained in this document represents no statement, promise or guarantee by Wyeth Pharmaceuticals concerning levels of reimbursement, payment or charge. Similarly, all Current Procedural Terminology & Healthcare Common Procedure Coding System (HCPCS) billing codes are supplied for information purposes only and represent no statement, promise or guarantee by Wyeth Pharmaceuticals that these codes will be appropriate or that reimbursement will be made.

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Introduction

Wyeth Pharmaceuticals developed this guide to assist providers with understanding coding, coverage, and payment of TORISEL® (temsirolimus) for key payers and provider types. The FDA approved TORISEL for the treatment of patients with advanced renal cell carcinoma (RCC). TORISEL is an mTOR inhibitor administered once a week as an IV infusion. TORISEL may be used in a variety of settings including the following sites of care:

- Physician office
- Freestanding infusion centers
- Hospital outpatient
- Hospital inpatient

The information provided in this guide supplies a general overview of reimbursement issues for these sites of care. Reimbursement is often complex, and payment methodologies continue to evolve across all payers. Checking with specific payers regarding local reimbursement policies is recommended.

If you have additional questions, please contact the TORISEL Reimbursement Support Program to receive the most current information about reimbursement and billing for TORISEL.

Important Safety Information

- Hypersensitivity reactions manifested by symptoms, including, but not limited to anaphylaxis, dyspnea, flushing, and chest pain have been observed with TORISEL.
- Serum glucose, serum cholesterol, and triglycerides should be tested before and during treatment with TORISEL.
 - The use of TORISEL is likely to result in hyperglycemia and hyperlipemia. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy and/or lipid-lowering agents, respectively.
- The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.
- Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic and others presented with symptoms. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics.
- Cases of fatal bowel perforation occurred with TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen.
- Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period.
- Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

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Important Safety Information (cont)

- Live vaccinations and close contact with those who received live vaccines should be avoided.
- Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped.
- The most common (incidence $\geq 30\%$) adverse reactions observed with TORISEL are: rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence $\geq 30\%$) are anemia (94%), hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).
- In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every 2 weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion.
- Most common grades 3/4 adverse events and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.
- St. John's Wort may decrease TORISEL plasma concentrations, and grapefruit juice may increase plasma concentrations of the major metabolite of TORISEL, and therefore both should be avoided.
- The combination of TORISEL and sunitinib resulted in dose-limiting toxicity (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization).

Contact Information:

TORISEL® Reimbursement Support Program

PO Box 220907

Charlotte, NC 28222-0907

Phone: **1-866-WYETH-ONC** (1-866-993-8466)

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Monday – Friday, 9:00 am – 6:00 pm, Eastern Time



Coding Overview

Payers and providers use coding systems to identify diagnoses, procedures, services, drugs, pharmaceutical devices, equipment, and other health-related items and services. Proper coding is an integral component to receiving appropriate reimbursement for TORISEL® (temsirolimus) and related services. Submitting inaccurate or incomplete codes may result in payment delays and incorrect payment levels. The majority of payers use nationally recognized code sets to report medical conditions, services, and drugs.

Site of Service

TORISEL may be administered in the following sites of care:

- Physician office
- Freestanding infusion centers
- Hospital outpatient
- Hospital inpatient

Depending on the site of service in which TORISEL is administered, providers may use different types of codes.

Site of Service	Code Sets Used
Physician Office/ Freestanding Infusion Centers	ICD-9-CM Diagnosis Codes* HCPCS Codes† CPT Codes‡
Hospital Outpatient	ICD-9-CM Diagnosis Codes HCPCS Codes CPT Codes Revenue Codes§
Hospital Inpatient	ICD-9-CM Diagnosis and Procedure Codes Revenue Codes

* International Classification of Diseases, 9th Revision, Clinical Modification 6th Edition, 2007 Expert, Ingenix, 2006

† Healthcare Common Procedure Coding System Level II, 2007 Expert, Ingenix, 2006

‡ Current Procedural Terminology CPT 2007, Professional Edition, American Medical Association, 2006

§ National Uniform Billing Committee (NUBC), American Hospital Association, 2007

ICD-9-CM Diagnosis Coding

Claims submitted for TORISEL® (temsirolimus) require an ICD-9-CM diagnosis code to report the patient's specific condition. The diagnosis codes that most accurately represent the patient's condition should be reported on the claim form and should reflect the conditions documented in the patient's medical record. The diagnosis code below may apply to patients with advanced renal cell carcinoma (RCC):

ICD-9-CM Diagnosis Code	Description
189.X	Malignant neoplasm of kidney and other and unspecified urinary organs

The diagnosis code selected should reflect the highest level of specificity available. When reporting advanced RCC, providers should indicate a fourth digit in place of the X to identify the etiology of the cancer:

- 0** - Kidney, except pelvis
- 1** - Renal pelvis

ICD-9-CM Procedure Coding

ICD-9-CM diagnosis codes identify why a patient needs treatment and report what services are provided. Hospitals use ICD-9-CM procedure codes to report the administration of drugs such as TORISEL. Hospitals may use the following ICD-9-CM procedure code to report the administration of TORISEL:

ICD-9-CM Procedure Code	Description
99.25	Injection or infusion of cancer chemotherapeutic substance

Coding for Drug Administration

All payers use CPT codes to determine reimbursement for professional services (including drug administration) provided in outpatient settings like physician offices and hospital outpatient departments.

TORISEL® (temsirolimus) is administered once a week by intravenous infusion, lasting between 30 to 60 minutes. When billing Medicare, Medicaid, or private payers for the administration of TORISEL in the outpatient setting, the following CPT codes may be appropriate:

Table 4. Administration Codes for TORISEL	
CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (list separately in addition to code for primary procedure)

Providers should follow payer-specific guidelines when coding for the administration of TORISEL.

HCPCS Coding for TORISEL

National Healthcare Common Procedure Coding System (HCPCS) codes, or J-codes, are typically used to report items such as drugs administered incident to provider services, medical equipment, and supplies.

Physician Office/Freestanding Infusion Center (Medicare and non-Medicare payers)

As of January 1, 2009, the J-code for TORISEL is:

○ **J9330, temsirolimus (TORISEL), 1 mg**

1 mg = 1 billable unit

Consult with the payer regarding specific claim and documentation requirements.

Hospital Outpatient (Medicare only)

Outpatient facilities should use the standard product J-code for billing once this has been established. Hospitals are required to use C-codes for products without established J-codes to allow for separate drug reimbursement under a provision known as transitional pass-through payments. This is often done so hospitals don't lose money on new therapeutics that become available for specific diseases and generally stops when the product receives an HCPCS code.

Providers are encouraged to check with payers for actual reimbursement methodologies, payment amounts, and claim submission requirements. It is important to review relevant contracts to determine patient-specific benefits, payment policies, and procedures.

Revenue Codes

Revenue codes categorize services provided in the hospital by revenue center. For Medicare claims, revenue codes must be included for each service on the UB-04 (CMS-1450) claim form. Many Medicaid programs and private payers also require revenue codes.

The following are examples of revenue codes that may be relevant to the administration of TORISEL® (temsirolimus) in the hospital setting.

Table 5. Examples of Revenue Codes Related to TORISEL	
Revenue Code	Description
510 (0510)	Clinic/General
636 (0636)	Drugs requiring detailed coding
331 (0331)	Chemotherapy, injected

Evaluation and Management Services

In some instances, a physician may bill for an evaluation and management (E/M) or office visit in addition to billing for the drug and administration services. Typically, a separate and identifiable procedure from the drug administration service must be performed to bill for a separate E/M service. The separate service must be clearly documented in the patient's medical record. Selection of an E/M code may be based on the following criteria:

- Patient status (new or established)
- Level of decision making required
- Complexity of the case
- Time spent directly with the patient

The following table outlines evaluation and management CPT codes for an established patient in the office or other outpatient visit setting:

Code	Description
99211*	Evaluation and management (Level 1) of an established patient that may not require the presence of a physician. Usually the presenting problems are minimal.
99212	Evaluation and management (Level 2) of an established patient that requires at least two of these three key components: a problem-focused history, a problem-focused examination, and straightforward medical decision making.
99213	Evaluation and management (Level 3) of an established patient that requires at least two of these three key components: an expanded problem-focused history, an expanded problem-focused examination, and medical decision making of low complexity.
99214	Evaluation and management (Level 4) of an established patient that requires at least two of these three key components: a detailed history, a detailed examination, and medical decision making of moderate complexity.
99215	Evaluation and management (Level 5) of an established patient that requires at least two of these three key components: a comprehensive history, a comprehensive examination, and medical decision making of high complexity.

*Please note that Medicare will not allow CPT code 99211 to be billed on the same date of service as a drug administration code.

When an E/M service is billed in addition to other professional services, a modifier may be required to indicate that a significant, separately identifiable service was performed:

-25, *Significant, separately identifiable evaluation and management service by the same physician on the same day of the procedure or other service.*

Providers should consult with individual payers to identify the appropriateness of billing for an office visit on the same day as other physician services.

Physician Office/Freestanding IV Infusion Center

Most public and private insurers will cover and reimburse for TORISEL® (temsirolimus) when it is provided in a physician's office or freestanding IV infusion center. However, payer requirements for coding, coverage, and payment of TORISEL will vary and should be verified prior to administration.

Coding

In the physician office or freestanding IV infusion center, the following codes may be used when billing for TORISEL and its administration:

- ICD-9-CM Diagnosis Code
- HCPCS Codes
- CPT Codes

Diagnosis Coding

Physician offices or freestanding IV infusion centers use ICD-9-CM diagnosis codes to report diseases and conditions. ICD-9-CM diagnosis codes identify why a patient needs treatment by documenting the medical necessity for administering TORISEL. At least one primary ICD-9-CM code is required on all CMS-1500 claim forms. The diagnosis that most accurately represents the patient's condition as documented in the patient's medical record should be reported on the claim form. The diagnosis code below may apply to patients with advanced RCC.

Table 7. ICD-9-CM Diagnosis Code for Advanced Renal Cell Carcinoma

ICD-9-CM Diagnosis Code	Description
189.X	Malignant neoplasm of kidney and other and unspecified urinary organs

The diagnosis code selected should reflect the highest level of specificity available. When reporting advanced RCC, providers should indicate a fourth digit in place of the X to identify the etiology of the cancer:

- 0** - Kidney, except pelvis
- 1** - Renal pelvis

Coding for TORISEL® (temsirolimus) (Medicare, Private Payers, and some Medicaid programs)

Medicare, Medicaid, and private payers use HCPCS codes for reporting specific services, supplies, medical equipment, and drugs.

As of January 1, 2009, the J-code for TORISEL is:

○ **J9330, temsirolimus (TORISEL), 1 mg**

1 mg = 1 billable unit

It is important to check with local payers regarding specific documentation and claim information requirements.

Coding for Drug Administration Services (Medicare Part B, Medicaid, and Private Payers)

In the physician office and freestanding IV infusion center settings, Medicare, Medicaid, and most private payers use CPT codes to bill for the administration of IV infusion services.

Table 8. Administration Codes for TORISEL® (temsirolimus)	
CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (list separately in addition to code for primary procedure)

Under some circumstances, physicians may also be able to bill for a separate E/M, or office visit service, in addition to the drug infusion. The additional service must be separate and identifiable from the drug infusion service and should be documented in the patient's medical record. There are several factors to consider in deciding which E/M code to use:

- Patient status (new or established)
- Level of decision making required
- Complexity of the case
- Amount of time spent with the patient

The following table outlines E/M codes for an established patient.

Table 9. Evaluation and Management CPT Codes	
Code	Description
99211*	Evaluation and management (Level 1) of an established patient that may not require the presence of a physician. Usually the presenting problems are minimal.
99212	Evaluation and management (Level 2) of an established patient that requires at least two of these three key components: a problem-focused history, a problem-focused examination, and straightforward medical decision making.
99213	Evaluation and management (Level 3) of an established patient that requires at least two of these three key components: an expanded problem-focused history, an expanded problem-focused examination, and medical decision making of low complexity.
99214	Evaluation and management (Level 4) of an established patient that requires at least two of these three key components: a detailed history, a detailed examination, and medical decision making of moderate complexity.
99215	Evaluation and management (Level 5) of an established patient that requires at least two of these three key components: a comprehensive history, a comprehensive examination, and medical decision making of high complexity.

*Please note that Medicare will not allow CPT code 99211 to be billed on the same date of service as a drug administration code.

Some payers will require providers to use a modifier to demonstrate that the E/M procedure was a separate service from other services rendered on the same date:

-25, *Significant, separately identifiable evaluation and management service by the same physician on the same day of the procedure or other service*

Providers should consult with individual payers to identify the appropriateness of billing for an office visit on the same day as other physician services.

Coverage and Payment

Medicare Part B

Medicare typically covers drugs used in the physician office and freestanding IV infusion centers that meet the following criteria:

- FDA approved
- Administered incident to a physician's service
- Used for a medically necessary purpose

Based on these criteria, TORISEL® (temsirolimus) is eligible for Medicare coverage in the physician office or freestanding IV infusion center.

Medicare reimbursement for physician-administered injectable products such as TORISEL is typically based on 106% of the average sales price (ASP). CMS calculates a drug's ASP using sales data submitted by drug manufacturers. These calculations are usually published by CMS at the start of each quarter. There is an approximate 3-6 month time lag between the time a price increase becomes official and when it is reflected in the ASP calculations.

Medicare reimburses physicians according to the Physician Fee Schedule for professional services provided to patients. The fee schedule is updated annually. Medicare assigns each covered CPT code a fee schedule amount.

Table 10. Administration Codes for TORISEL® (temsirolimus)

CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (list separately in addition to code for primary procedure)

Medicaid

TORISEL® (temsirolimus) will generally be covered by Medicaid when administered in the physician's office and freestanding IV infusion centers. Coverage policies and reimbursement for TORISEL and associated services vary from state to state.

The majority of Medicaid programs use a fee schedule to reimburse physicians and freestanding IV infusion centers for the administration services associated with TORISEL. Additionally, state Medicaid programs typically reimburse drugs separately from administration service using a variety of methodologies:

- A percentage of average wholesale price (AWP)
- A percentage of wholesale acquisition cost (WAC)
- A percentage of ASP
- Acquisition/invoice cost

Check with your state Medicaid agency for actual reimbursement methodologies, payment amounts, and claim submission requirements.

Some Medicaid programs are beginning to require National Drug Code (NDC) and quantity information in the shaded area of Box 24 of the CMS-1500 form in addition to the J-code. This information is in addition to the CPT/HCPCS codes that are still required. As with all payers, each state has different requirements. Please check with your local Medicaid program to verify their coding specifications.

Private Payers

Medical services rendered in the physician office or freestanding IV infusion center are generally covered by most private plans, although network or coverage restrictions vary. Most private payers will cover TORISEL when administered in these settings.

Reimbursement methodologies can vary dramatically by payer, plan type, and contract provisions. Private payers typically reimburse physician services based on a fee schedule. They may reimburse physician-administered injectable drugs such as TORISEL separately through various means such as:

- A percentage of AWP
- A percentage of WAC
- A percentage of ASP
- Acquisition/invoice cost

It is important to review private payer contracts to determine patient-specific benefits, payment policies, and procedures. Contacting payers directly to understand the coding, coverage, and payment requirements is recommended.

Hospital Outpatient

Most public and private payers cover and reimburse health care professionals for TORISEL® (temsirolimus) when it is administered in a hospital outpatient facility. The following codes may be used in the hospital outpatient setting when billing for TORISEL and its administration:

- ICD-9-CM Diagnosis Codes
- HCPCS Codes
- CPT Codes
- Revenue Codes

Diagnosis Coding

ICD-9-CM diagnosis codes are used in the hospital outpatient setting to report diagnoses. The codes identify why patients need treatments such as TORISEL. At least one ICD-9-CM code is required on all claim forms. The diagnosis code below may apply to patients with advanced RCC:

ICD-9-CM Diagnosis Code	Description
189.X	Malignant neoplasm of kidney and other and unspecified urinary organs

The diagnosis code selected should reflect the highest level of specificity available. When reporting advanced RCC, providers should indicate a fourth digit in place of the X to identify the etiology of the cancer:

- 0** - Kidney, except pelvis
- 1** - Renal pelvis

The diagnosis, as documented in the patient's medical record, that most accurately reflects the patient's condition should be reported on the claim form.

Coding for TORISEL® (temsirolimus) (Medicare)

Outpatient facilities should use the standard product J-code for billing once this has been established. Hospitals are required to use C-codes for products without established J-codes to allow for separate drug reimbursement under a provision known as transitional pass-through payments. This is often done so hospitals don't lose money on new therapeutics that become available for specific diseases and generally stops when the product receives an HCPCS code.

Providers are encouraged to check with payers for actual reimbursement methodologies, payment amounts, and claim submission requirements. It is important to review relevant contracts to determine patient-specific benefits, payment policies, and procedures.

Coding for TORISEL (Private Payers and Some Medicaid Programs)

As of January 1, 2009, the J-code for TORISEL is:

○ **J9330, temsirolimus (TORISEL), 1 mg**

1 mg=1 billable unit

It is advisable to check with individual payers to determine appropriate coding, billing, and documentation requirements for submitting claims.

Coding for Drug Administration Services (Medicare, Medicaid, and Private Payers)

TORISEL® (temsirolimus) is administered once a week by intravenous infusion that typically lasts 30 to 60 minutes. When billing Medicare, Medicaid, or private payers for the administration of TORISEL in the hospital outpatient setting, providers may use the following codes:

Table 12. Administration Codes for TORISEL® (temsirolimus)	
CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (list separately in addition to code for primary procedure)

Providers should select the most appropriate codes and units based on the actual length of the infusion.

Revenue Codes

Each line item on a UB-04 (CMS-1450) claim form must be accompanied by a revenue code. Revenue codes allow hospitals to capture cost data by hospital department. Medicare uses these codes for cost reporting, but many Medicaid programs and private payers also require revenue codes on outpatient hospital claims.

The following are examples of revenue codes that may be relevant to the administration of TORISEL® (temsirolimus) in the hospital outpatient setting:

Table 13. Examples of Revenue Codes Related to TORISEL	
Revenue Code	Description
510 (0510)	Clinic/General
636 (0636)	Drugs requiring detailed coding
331 (0331)	Chemotherapy, injected

Hospitals should indicate the most specific revenue code available on the claim form.

Coverage and Payment

Medicare

Medicare Part B reimburses hospital outpatient facilities based on a prospective payment system that uses Ambulatory Payment Classifications (APCs). Under the APC system, services that are comparable clinically and in terms of resource costs are packaged or grouped together. These packages of similar services are known as APCs. Hospital outpatient facilities can receive multiple APC payments for one patient encounter, depending upon the types of services provided.

The infusion procedure for TORISEL® (temsirolimus) is eligible for reimbursement by Medicare. The table below reflects the codes associated with the administration of TORISEL in the hospital outpatient setting, the APCs to which these codes map, and the APC descriptions:

CPT Code	Maps to APC	APC Description
96413	0441	Level VI Drug Administration
96415	0438	Level III Drug Administration

Drugs administered in the hospital outpatient setting may be reimbursed separately from other procedures. Medicare typically reimburses drugs eligible for separate payment based on 106% of ASP.

Medicaid

TORISEL is generally eligible for Medicaid reimbursement in the hospital outpatient setting. Coverage and reimbursement for TORISEL and associated services in the hospital outpatient setting varies for each state because Medicaid policy is developed at the state level.

State Medicaid programs use a variety of methodologies to reimburse for hospital outpatient services, such as drug administration. Payment methodologies include the following:

- Ambulatory Payment Groups
- Discounted charges
- Fee schedules
- Per diem rates

Some Medicaid programs include payment for drugs in these rates. However, some states reimburse drugs administered in the hospital outpatient setting separately from the administration services. If the state Medicaid program reimburses TORISEL® (temsirolimus) separately from the administration service, payment may be based on one of the following:

- A percentage of AWP
- A percentage of WAC
- A percentage of ASP
- Acquisition/invoice cost

Check with your state Medicaid agency for actual reimbursement methodologies, payment amounts, and claim submission requirements.

Private Payers

Hospital outpatient services are generally a standard, covered benefit for most private plans. Most private payers will cover TORISEL when administered in the hospital outpatient setting.

Reimbursement methodologies for hospital outpatient services will vary by payer, plan type, and contract provisions between plans and hospitals. Private payers may reimburse hospital outpatient services based on the following:

- Discounted charges
- Fee schedules
- Per diem rates

Drugs administered in the hospital outpatient setting may be reimbursed separately from administration services. Payment for drugs may be based on one of the following:

- A percentage of AWP
- A percentage of WAC
- A percentage of ASP
- Acquisition/invoice cost

Check with specific payers for actual reimbursement methodologies, payment amounts, and claim submission requirements.

It is important to review relevant contracts to determine patient-specific benefits, payment policies, and procedures. You may also contact the payer directly to understand the coding, coverage, and payment requirements.

Hospital Inpatient

Most public and private payers will cover and reimburse for TORISEL® (temsirolimus) when it is provided in an inpatient hospital facility. However, payer requirements for coding, coverage, and payment of TORISEL will vary and should be verified with each payer.

Coding

Patients are classified according to diagnosis, type of treatment, and other relevant criteria through the ICD-9-CM coding system in the hospital inpatient setting. The following codes are typically used in the hospital inpatient setting when billing for TORISEL and its administration:

- ICD-9-CM Diagnosis and Procedure Codes
- Revenue Codes

ICD-9-CM Diagnosis Coding

Hospital inpatient facilities use ICD-9-CM codes to report diagnoses and procedures. ICD-9-CM diagnosis codes identify why a patient needs treatment by documenting the medical necessity for administering TORISEL. At a minimum, one ICD-9-CM code is required on all claim forms.

ICD-9-CM Diagnosis Code	Description
189.X	Malignant neoplasm of kidney and other and unspecified urinary organs

The diagnosis code selected for billing purposes should reflect the highest level of specificity available as documented in the patient medical record. When reporting advanced RCC, providers should indicate a fourth digit in place of the X to identify the etiology of the cancer:

- 0** - Kidney, except pelvis
- 1** - Renal pelvis

Procedure Coding

While ICD-9-CM diagnosis codes indicate why a patient needs treatment, ICD-9-CM procedure codes report what services are provided during the hospital inpatient stay. Hospitals use ICD-9-CM procedure codes to report the administration of drugs such as TORISEL® (temsirolimus).

Table 16. ICD-9-CM Procedure Code	
ICD-9-CM Procedure Code	Description
99.25	Injection or infusion of cancer chemotherapeutic substance

Revenue Codes

Each line item on a UB-04 (CMS-1450) claim form must be accompanied by a revenue code. Revenue codes allow hospitals to capture cost data by hospital department. Medicare uses these codes for cost reporting, but many Medicaid programs and private payers also require revenue codes on hospital claim forms.

The revenue codes listed below are examples of codes that may be relevant to the administration of TORISEL in the hospital inpatient setting.

Table 17. Examples of Revenue Codes Related to TORISEL® (temsirolimus)	
Revenue Code	Description
510 (0510)	Clinic/General
636 (0636)	Drugs requiring detailed coding
331 (0331)	Chemotherapy, injected

Hospitals should indicate the most specific revenue code available on the claim form.

Coverage and Payment

Medicare

Medicare provides coverage of medications and services administered in the inpatient hospital setting through Part A. Criteria that need to be met in order for Medicare to cover drugs such as TORISEL® (temsirolimus) include the following:

- Use of the drug must be safe and effective and otherwise reasonable and necessary
- Drug or biological must represent a cost to the facility rendering services to the beneficiary

Medicare reimburses inpatient hospital services under the hospital inpatient prospective payment system (IPPS), which bases payment on diagnosis-related groups (DRGs).^{*} The DRG payment system reimburses the hospital according to the level of resources required to treat patients with similar diagnoses undergoing similar treatments. The payment rate for a DRG is hospital-specific, and all services and supplies provided during a hospital stay, including medications, are included in the fixed reimbursement rate. Therefore, TORISEL will not be reimbursed separately in the hospital inpatient setting.

The following is an example of a DRG that Medicare could assign to patients diagnosed with advanced renal cell carcinoma:

- **318, Kidney and urinary tract neoplasms with CC**
- **303, Kidney, ureter, and bladder procedures for neoplasm**

Medicaid

Like Medicare, Medicaid programs may use DRG systems to reimburse hospitals for services provided, but payment rates may vary from those for Medicare. Medicaid coverage and payment for services provided in the hospital inpatient setting varies by state. Medicaid programs may also base payment on other prospective payment rates such as case rates, discounted charges, or per diem rates. States with prospective payment systems typically do not provide separate reimbursement for drugs.

Private Payers

Many private payers reimburse hospital facilities using a per diem methodology in which all services, supplies, and medications are included in one comprehensive daily rate. Other commercial plans base payment on Medicare's DRG system, case rates, discounted charges, or capitated rates. Payers that use per diem or case rates typically do not provide separate payment for drugs. Payment methods used by private payers for hospital inpatient services also vary.

^{*} DRG Expert 2007, 23rd Edition, Ingenix, 2006.

Support Materials

Tips for Successful Claims Filing

Understanding coding and coverage guidelines will assist with obtaining appropriate reimbursement for TORISEL® (temsirolimus). Claims may be denied as a result of the following:

- Incorrect codes or modifiers
- Incorrect units
- Omission of proper documentation supporting the medical necessity of the service
- Filing claims outside of established time limits

It is strongly recommended that you contact individual payers to verify appropriate coding and specific coverage guidelines for TORISEL and its administration. If you need assistance with verifying benefits for TORISEL or have other reimbursement questions, please contact:

TORISEL® Reimbursement Support Program

PO Box 220907

Charlotte, NC 28222-0907

Phone: **1-866-WYETH-ONC** (1-866-993-8466)

Fax: 1-866-993-8411

Monday – Friday, 9:00 am – 6:00 pm, Eastern Time

Sample Claim Denial Appeal Letter for TORISEL® (tamsirolimus)

Claims for advanced renal cell carcinoma can be denied for a variety of reasons and may be appealed with the payer. The TORISEL Reimbursement Support Program can provide assistance with the appeals process. In most cases, payers will require detailed information about the patient and the product before reconsidering a denied claim. Understanding the reason for the denial will help ensure that the proper documentation is submitted and is an integral part of the appeals process. Below is a sample appeal letter designed as a guidance tool that may be used after confirming the denial issue with the provider.

[Date]

[Payer Name]

[Payer Address]

[City], [State] [ZIP Code]

RE: **[Patient Name]**
[Patient Address]
[Patient Policy ID #]
[Claim Number]
[Date(s) of Service]

Dear **[Contact Name]**:

This correspondence serves as a request for reconsideration of payment of a denied claim for TORISEL® (tamsirolimus) administered to **[Patient Name]** on **[Date(s) of Service]**.

This patient has been under my care for the treatment of **[Patient Diagnosis]**. You have indicated that TORISEL is not covered because **[Reason for Denial]**.

TORISEL is an FDA-approved product.

TORISEL has been administered as a medically necessary part of this patient's treatment. I would appreciate reconsideration of coverage for the **[Date(s) of Service]** claim for **[Patient Name]**. Please contact me at **[Physician Phone Number]** if you require additional information.

Sincerely,

[Physician Name]

[Practice Name]

Enc [Attach original claim form, denial/Explanation of Benefits (EOB), additional supporting documents such as information regarding the patient's treatment with TORISEL, including medical history, diagnosis, lab results, and the treatment plan.]

Overview of TORISEL® (temsirolimus) Reimbursement Support Program

The TORISEL Reimbursement Support Program has been designed to assist with billing and reimbursement of TORISEL therapy. In addition to live customer support provided by reimbursement counselors, a variety of resources are offered.

Reimbursement Services: The reimbursement services provided by the TORISEL Reimbursement Support Program are designed to ease the administrative burden providers may face when working with patients' insurers. Services include:

- Research into patient-specific coverage for TORISEL
- Identification of TORISEL coverage policies for federal, state, and private payers
- Research to identify alternatives for patients with inadequate or no coverage, including assessment of the patient's eligibility to participate in the TORISEL Patient Assistance Program
- Comprehensive prior authorization support
- Coding and claims filing assistance
- Claims tracking assistance to routinely monitor status of TORISEL claims
- Claims denial appeal assistance

Patient Assistance Program: The TORISEL Reimbursement Support Program offers product for patients who lack adequate coverage for TORISEL and meet program guidelines.

- To determine if a patient qualifies for assistance, submit the Patient Enrollment Form and HIPAA Authorization. (Providers seeking assistance for the first time will be asked to complete the one-time Physician Enrollment Form.)
- A dedicated Regional Reimbursement Consultant (RRC) will review the patient's eligibility and can usually provide a response within 2 business days of receiving the completed enrollment form.
- Eligible patients receive assistance in the form of free product, which is distributed on a monthly basis to the treating provider.

Product Replacement Program: The TORISEL® (temsirrolimus) Patient Assistance Program allows for product replacement under certain circumstances. Product replacement is available for patients who have been provided TORISEL and who then have their insurance claims fully denied after an appeal. If the patient met the other eligibility criteria for the Patient Assistance Program at the time TORISEL was administered, the product the patient received may be replaced.

- The provider and patient will be asked to submit the same applications as the Patient Assistance Program.
- The RRC will review the patient's eligibility, including investigation of the patient's insurance benefits.
- Your RRC can provide further details and requirements for the availability of product replacement.

Contact Information:

TORISEL® Reimbursement Support Program

PO Box 220907

Charlotte, NC 28222-0907

Phone: **1-866-WYETH-ONC** (1-866-993-8466)

Fax: 1-866-993-8411

Monday – Friday, 9:00 am – 6:00 pm, Eastern Time



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TORISEL® safely and effectively. See full prescribing information for TORISEL.

TORISEL Kit (temsirolimus) injection, for intravenous infusion only

Initial U.S. approval: 2007

INDICATIONS AND USAGE

TORISEL® is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)
- Antihistamine pre-treatment is recommended. (2.2)
- TORISEL (temsirolimus) injection vial contents must first be diluted with the enclosed diluent before diluting the resultant solution with 250 mL of 0.9% sodium chloride injection. (2.5)

DOSAGE FORMS AND STRENGTHS

TORISEL injection, 25 mg/mL supplied with DILUENT for TORISEL®. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- To treat hypersensitivity reactions stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.2, 5.5)
- Infections may result from immunosuppression. (5.3)
- Monitor for symptoms or radiographic changes of interstitial lung disease (ILD). If ILD is suspected, discontinue

TORISEL, and consider use of corticosteroids and/or antibiotics. (5.4)

- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.6)
- Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.7)
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.8)
- Live vaccinations and close contact with those who received live vaccines should be avoided. (5.12)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 30\%$) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence $\geq 30\%$) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Strong inducers of CYP3A4/5 and inhibitors of CYP3A4 may affect concentrations of the primary metabolite of TORISEL. If alternatives cannot be used, dose modifications of TORISEL are recommended. (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TORISEL is indicated for the treatment of advanced renal cell carcinoma.

2 DOSAGE AND ADMINISTRATION

2.1 Advanced Renal Cell Carcinoma

The recommended dose of TORISEL for advanced renal cell carcinoma is 25 mg infused over a 30-60 minute period once a week.

Treatment should continue until disease progression or unacceptable toxicity occurs.

2.2 Premedication

Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL [see *Hypersensitivity Reactions (5.1)*].

2.3 Dosage Interruption/Adjustment

TORISEL should be held for absolute neutrophil count (ANC) < 1,000/mm³, platelet count < 75,000/mm³, or NCI CTCAE grade 3 or greater adverse reactions. Once toxicities have resolved to grade 2 or less, TORISEL may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

2.4 Dose Modification Guidelines

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TORISEL dose reduction to 12.5 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TORISEL dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor. [see *Drug Interactions (7.2)*]

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the temsirolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer. [see *Drug Interactions (7.1)*]

2.5 Instructions for Preparation and Administration

TORISEL must be stored under refrigeration at 2°-8°C (36°-46°F) and protected from light. During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

In order to minimize the patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TORISEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Dilution:

In preparing the TORISEL administration solution, follow this two-step dilution process in an aseptic manner.

Step 1:

Inject 1.8 mL of DILUENT for TORISEL® into the vial of TORISEL (temsirolimus) injection (25 mg/ml). The TORISEL (temsirolimus) vial contains an overfill of 0.2 mL (30 mg/1.2 mL). Due to the intentional overfill in the TORISEL injection vial, the drug concentration of the resulting solution will be 10 mg/mL. A total volume of 3 mL will be obtained including the overfill. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates. The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature.

Step 2:

Withdraw the required amount of temsirolimus from the 10 mg/mL drug solution/diluent mixture prepared in Step 1. Inject rapidly into a 250 mL container (glass, polyolefin, or polyethylene) of 0.9% sodium chloride injection. Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

Administration:

- The sodium chloride injection container should be composed of non-DEHP containing materials, such as glass, polyolefin or polyethylene, and the administration set should consist of non-DEHP tubing to avoid extraction of di-(2-ethylhexyl) phthalate (DEHP). TORISEL contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from PVC.
- An inline polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration.
- The final diluted solution of TORISEL is intravenously infused over a 30-60 minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the drug.
- Administration of the final diluted infusion solution should be completed within six hours from the time that the drug solution/diluent mixture is added to the sodium chloride injection.

Compatibilities and Incompatibilities

Undiluted TORISEL injection should not be added directly to aqueous infusion solutions. Direct addition of TORISEL injection to aqueous solutions will result in precipitation of drug. Always combine TORISEL injection with DILUENT for TORISEL® before adding to infusion solutions. It is recommended that TORISEL be administered in 0.9% sodium chloride injection after combining with diluent. The stability of TORISEL in other infusion solutions has not been evaluated. Addition of other drugs or nutritional agents to admixtures of TORISEL in sodium chloride injection has not been evaluated and should be avoided. Temsirolimus is degraded by both

acids and bases, and thus combinations of temsirolimus with agents capable of modifying solution pH should be avoided.

3 DOSAGE FORMS AND STRENGTHS

TORISEL (temsirolimus) is supplied as a kit consisting of the following:

TORISEL (temsirolimus) injection (25 mg/ml). The TORISEL vial includes an overfill of 0.2 mL.

DILUENT for TORISEL®. The DILUENT vial includes a deliverable volume of 1.8 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, and chest pain have been observed with TORISEL.

TORISEL should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of TORISEL.

An H₁ antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORISEL should be used with caution in patients with known hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.

If a patient develops a hypersensitivity reaction during the TORISEL infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H₁-receptor antagonist (such as diphenhydramine), if not previously administered [see *Dosage and Administration (2.2)*], and/or an H₂-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the TORISEL infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).

5.2 Hyperglycemia/Glucose Intolerance

The use of TORISEL is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving TORISEL had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy. Serum glucose should be tested before and during treatment with TORISEL. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

5.3 Infections

The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections [see *Adverse Reactions (6.1)*].

5.4 Interstitial Lung Disease

Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some

patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.

5.5 Hyperlipemia

The use of TORISEL is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving TORISEL had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with TORISEL.

5.6 Bowel Perforation

Cases of fatal bowel perforation occurred in patients who received TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen. Patients should be advised to report promptly any new or worsening abdominal pain or blood in their stools.

5.7 Renal Failure

Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL. Some of these cases were not responsive to dialysis.

5.8 Wound Healing Complications

Use of TORISEL has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of TORISEL in the perioperative period.

5.9 Intracerebral Hemorrhage

Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

5.10 Co-administration with Inducers or Inhibitors of CYP3A Metabolism

Agents Inducing CYP3A Metabolism:

Strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampacin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease TORISEL plasma concentrations unpredictably. Patients receiving TORISEL should not take St. John's Wort concomitantly. [see *Dosage and Administration (2.4)* and *Drug Interactions (7.1)*].

Agents Inhibiting CYP3A Metabolism:

Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may increase blood concentrations of the active metabolite sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered. [see *Dosage and Administration (2.4)* and *Drug Interactions (7.2)*].

5.11 Concomitant use of TORISEL with sunitinib

The combination of TORISEL and sunitinib resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization) were observed in two out of three patients treated in the first cohort of a phase 1 study at doses of TORISEL 15 mg IV per week and sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest).

5.12 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with TORISEL. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.13 Pregnancy

Pregnancy Category D

Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. Embryo-fetal adverse effects in rats consisted of reduced fetal weight and reduced ossifications, and in rabbits included reduced fetal weight, omphalocele, bifurcated sternabrae, notched ribs, and incomplete ossifications.

In rats, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of 2.7 mg/m²/day (approximately 0.04-fold the AUC in cancer patients at the human recommended dose). In rabbits, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of ≥7.2 mg/m²/day (approximately 0.12-fold the AUC in cancer patients at the recommended human dose).

Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped. Temsirolimus can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Men should be counseled regarding the effects of TORISEL on the fetus and sperm prior to starting treatment [see *Nonclinical Toxicology (13.1)*]. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of TORISEL.

5.14 Monitoring Laboratory Tests

In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every two weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion.

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with TORISEL in clinical trials and are discussed in greater detail in other sections of the label [see *Warnings and Precautions (5)*].

Hypersensitivity Reactions [see *Warnings and Precautions (5.1)*]

Hyperglycemia/Glucose Intolerance [see *Warnings and Precautions (5.2)*]

Interstitial Lung Disease [see *Warnings and Precautions (5.4)*]

Hyperlipemia [see *Warnings and Precautions (5.5)*]

Bowel Perforation [see *Warnings and Precautions (5.6)*]

Renal Failure [see *Warnings and Precautions (5.7)*]

The most common (≥ 30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥ 30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

In the Phase 3 randomized, open-label study of interferon alfa (IFN-α) alone, TORISEL alone, and TORISEL and IFN-α, a total of 616 patients were treated. Two hundred patients received IFN-α weekly, 208 received TORISEL 25 mg weekly, and 208 patients received a combination of TORISEL and IFN-α weekly [see *Clinical Studies (14)*].

Treatment with the combination of TORISEL 15 mg and IFN-α was associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in overall survival when compared with IFN-α alone.

Table 1 shows the percentage of patients experiencing treatment emergent adverse reactions. Reactions reported in at least 10% of patients who received TORISEL 25 mg alone or IFN-α alone are listed. Table 2 shows the percentage of patients experiencing selected laboratory abnormalities. Data for the same adverse reactions and laboratory abnormalities in the IFN-α alone arm are shown for comparison.

Table 1 – Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

Adverse Reaction	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	139 (67)	199 (100)	155 (78)
General disorders				
Asthenia	106 (51)	23 (11)	127 (64)	52 (26)
Edema ^a	73 (35)	7 (3)	21 (11)	1 (1)
Pain	59 (28)	10 (5)	31 (16)	4 (2)
Pyrexia	50 (24)	1 (1)	99 (50)	7 (4)
Weight Loss	39 (19)	3 (1)	50 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest Pain	34 (16)	2 (1)	18 (9)	2 (1)
Chills	17 (8)	1 (1)	59 (30)	3 (2)
Gastrointestinal disorders				
Mucositis ^b	86 (41)	6 (3)	19 (10)	0 (0)
Anorexia	66 (32)	6 (3)	87 (44)	8 (4)
Nausea	77 (37)	5 (2)	82 (41)	9 (5)
Diarrhea	56 (27)	3 (1)	40 (20)	4 (2)
Abdominal Pain	44 (21)	9 (4)	34 (17)	3 (2)
Constipation	42 (20)	0 (0)	36 (18)	1 (1)
Vomiting	40 (19)	4 (2)	57 (29)	5 (3)
Infections				
Infections ^c	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection ^d	31 (15)	3 (1)	24 (12)	3 (2)
Pharyngitis	25 (12)	0 (0)	3 (2)	0 (0)
Rhinitis	20 (10)	0 (0)	4 (2)	0 (0)
Musculoskeletal and connective tissue disorders				
Back Pain	41 (20)	6 (3)	28 (14)	7 (4)
Arthralgia	37 (18)	2 (1)	29 (15)	2 (1)
Myalgia	16 (8)	1 (1)	29 (15)	2 (1)

Table 1 – Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

Adverse Reaction	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	139 (67)	199 (100)	155 (78)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	58 (28)	18 (9)	48 (24)	11 (6)
Cough	53 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
Skin and subcutaneous tissue disorders				
Rash ^e	97 (47)	10 (5)	14 (7)	0 (0)
Pruritus	40 (19)	1 (1)	16 (8)	0 (0)
Nail Disorder	28 (14)	0 (0)	1 (1)	0 (0)
Dry Skin	22 (11)	1 (1)	14 (7)	0 (0)
Acne	21 (10)	0 (0)	2 (1)	0 (0)
Nervous system disorders				
Dysgeusia ^f	41 (20)	0 (0)	17 (9)	0 (0)
Insomnia	24 (12)	1 (1)	30 (15)	0 (0)
Depression	9 (4)	0 (0)	27 (14)	4 (2)

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.

- a Includes edema, facial edema, and peripheral edema
- b Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis
- c Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster
- d Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection
- e Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash
- f Includes taste loss and taste perversion

The following selected adverse reactions were reported less frequently (<10%).

Gastrointestinal Disorders – Fatal bowel perforation occurred in 1 patient (1%).

Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).

Immune System - Allergic/Hypersensitivity reactions occurred in 18 patients (9%).

Angioneurotic edema-type reactions have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

Infections - Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).

General Disorders and Administration Site Conditions - Impaired wound healing occurred in 3 patients (1%).

Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.

Vascular - Hypertension occurred in 14 patients (7%); venous

thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Table 2 – Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

Laboratory Abnormality	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Hemoglobin Decreased	195 (94)	41 (20)	180 (90)	43 (22)
Lymphocytes Decreased**	110 (53)	33 (16)	106 (53)	48 (24)
Neutrophils Decreased**	39 (19)	10 (5)	58 (29)	19 (10)
Platelets Decreased	84 (40)	3 (1)	51 (26)	0 (0)
Leukocytes Decreased	67 (32)	1 (1)	93 (47)	11 (6)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Creatinine Increased	119 (57)	7 (3)	97 (49)	2 (1)
Glucose Increased	186 (89)	33 (16)	128 (64)	6 (3)
Phosphorus Decreased	102 (49)	38 (18)	61 (31)	17 (9)
Total Bilirubin Increased	16 (8)	2 (1)	25 (13)	4 (2)
Total Cholesterol Increased	181 (87)	5 (2)	95 (48)	2 (1)
Triglycerides Increased	173 (83)	92 (44)	144 (72)	69 (35)
Potassium Decreased	43 (21)	11 (5)	15 (8)	0 (0)

*NCI CTC version 3.0

**Grade 1 toxicity may be under-reported for lymphocytes and neutrophils

7 DRUG INTERACTIONS

7.1 Agents Inducing CYP3A Metabolism

Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus C_{max} (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus C_{max} by 65% and AUC by 56% compared to TORISEL treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered [see *Dosage and Administration* (2.4)].

7.2 Agents Inhibiting CYP3A Metabolism

Co-administration of TORISEL with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus C_{max} or AUC; however, sirolimus AUC increased 3.1-fold, and C_{max} increased 2.2-fold compared to TORISEL alone. If alternative treatment cannot be administered, a dose adjustment should be considered. [see *Dosage and Administration* (2.4)].

7.3 Interactions with Drugs Metabolized by CYP2D6

The concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of TORISEL was co-administered. No clinically significant effect is anticipated when temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions* (5.13)].

8.3 Nursing Mothers

TORISEL® Kit (temsirolimus) injection

It is not known whether TORISEL is excreted into human milk, and due to the potential for tumorigenicity shown for sirolimus (active metabolite of TORISEL) in animal studies, a decision should be made whether to discontinue nursing or discontinue TORISEL, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TORISEL in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TORISEL did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

No clinical studies were conducted with TORISEL in patients with decreased renal function. Less than 5% of total radioactivity was excreted in the urine following a 25 mg intravenous dose of [¹⁴C]-labeled temsirolimus in healthy subjects. Renal impairment is not expected to markedly influence drug exposure, and no dosage adjustment of TORISEL is recommended in patients with renal impairment. TORISEL has not been studied in patients undergoing hemodialysis.

8.7 Hepatic Impairment

Temsirolimus is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction on temsirolimus disposition.

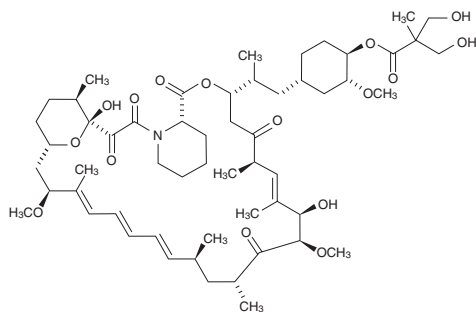
10 OVERDOSAGE

There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients with cancer in phase 1 and 2 trials with repeated intravenous doses as high as 220 mg/m². The risk of several serious adverse events, including thrombosis, bowel perforation, interstitial lung disease (ILD), seizure, and psychosis, is increased with doses of TORISEL greater than 25 mg.

11 DESCRIPTION

Temsirolimus, an inhibitor of mTOR, is an antineoplastic agent. Temsirolimus is a white to off-white powder with a molecular formula of C₅₆H₈₇NO₁₆ and a molecular weight of 1030.30. It is non-hygroscopic. Temsirolimus is practically insoluble in water and soluble in alcohol. It has no ionizable functional groups, and its solubility is independent of pH.

The chemical name of temsirolimus is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*a**S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34*a*-Hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4'-[2,2-bis(hydroxymethyl)propionate]; or Rapamycin, 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate].



TORISEL (temsirolimus) injection, 25 mg/mL, is a clear, colorless to yellow, non-aqueous, ethanolic, sterile solution. TORISEL (temsirolimus) injection requires two dilutions prior to intravenous infusion. TORISEL (temsirolimus) injection should be diluted only with the supplied DILUENT for TORISEL®.

DILUENT for TORISEL® is a sterile, non-aqueous solution that is supplied with TORISEL injection, as a kit.

TORISEL (temsirolimus) injection, 25 mg/mL:

Active ingredient: temsirolimus (25 mg/mL)

Inactive ingredients: dehydrated alcohol (39.5% w/v), *dl*-alpha-tocopherol (0.075% w/v), propylene glycol (50.3% w/v), and anhydrous citric acid (0.0025% w/v).

DILUENT for TORISEL®

Inactive ingredients: polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v) and dehydrated alcohol (19.9% w/v).

After the TORISEL (temsirolimus) injection vial has been diluted with DILUENT for TORISEL®, in accordance with the instructions in section 2.5, the solution contains 35.2% alcohol.

TORISEL (temsirolimus) injection and DILUENT for TORISEL® are filled in clear glass vials with butyl rubber stoppers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In *in vitro* studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

12.3 Pharmacokinetics

Absorption

Following administration of a single 25 mg dose of TORISEL in patients with cancer, mean temsirolimus C_{max} in whole blood was 585 ng/mL (coefficient of variation, CV =14%), and mean AUC in blood was 1627 ng·h/mL (CV=26%). Typically C_{max} occurred at the end of infusion. Over the dose range of 1 mg to 25 mg, temsirolimus exposure increased in a less than dose proportional manner while sirolimus exposure increased proportionally with dose. Following a single 25 mg intravenous dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus.

Distribution

Following a single 25 mg intravenous dose, mean steady-state volume of distribution of temsirolimus in whole blood of patients with cancer was 172 liters. Both temsirolimus and sirolimus are extensively partitioned into formed blood elements.

Metabolism

Cytochrome P450 3A4 is the major isozyme responsible for the formation of five temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the

metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes temsirolimus was an inhibitor of CYP2D6 and 3A4. However, there was no effect observed *in vivo* when temsirolimus was administered with desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

Elimination

Elimination is primarily via the feces. After a single IV dose of [¹⁴C]-temsirolimus approximately 82% of total radioactivity was eliminated within 14 days, with 4.6% and 78% of the administered radioactivity recovered in the urine and feces, respectively. Following a single 25 mg dose of TORISEL in patients with cancer, temsirolimus mean (CV) systemic clearance was 16.2 (22%) L/h. Temsirolimus exhibits a bi-exponential decline in whole blood concentrations and the mean half-lives of temsirolimus and sirolimus were 17.3 hr and 54.6 hr, respectively.

Effects of Age and Gender

In population pharmacokinetic-based data analyses, no relationship was apparent between drug exposure and patient age or gender.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with temsirolimus. However, sirolimus, the major metabolite of temsirolimus in humans, was carcinogenic in mice and rats. The following effects were reported in mice and/or rats in the carcinogenicity studies conducted with sirolimus: lymphoma, hepatocellular adenoma and carcinoma, and testicular adenoma.

Temsirolimus was not genotoxic in a battery of *in vitro* (bacterial reverse mutation in *Salmonella typhimurium* and *Escherichia coli*, forward mutation in mouse lymphoma cells, and chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse micronucleus) assays.

In male rats, the following fertility effects were observed: decreased number of pregnancies, decreased sperm concentration and motility, decreased reproductive organ weights, and testicular tubular degeneration. These effects were observed at oral temsirolimus doses ≥ 3 mg/m²/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/m²/day.

In female rats, an increased incidence of pre- and post-implantation losses occurred at oral doses ≥ 4.2 mg/m²/day (approximately 0.3-fold the human recommended intravenous dose), resulting in decreased numbers of live fetuses.

14 CLINICAL STUDIES

A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving TORISEL or TORISEL plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly

assigned (1:1:1) to receive IFN-α alone (n=207), TORISEL alone (25 mg weekly; n=209), or the combination arm (n=210).

The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

The median duration of treatment in the TORISEL arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks). There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL 25 mg arm compared to IFN-α. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in overall survival when compared with IFN-α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 3.

Parameter	TORISEL n = 209	IFN-α n = 207	P-value ^a	Hazard Ratio (95% CI) ^b
Median Overall Survival Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0078*	0.73 (0.58, 0.92)
Median Progression-Free Survival Months (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	0.0001**	0.66 (0.53, 0.81)
Overall Response Rate % (95% CI)	8.6 (4.8, 12.4)	4.8 (1.9, 7.8)	0.1232** ^c	NA

CI = confidence interval; NA = not applicable

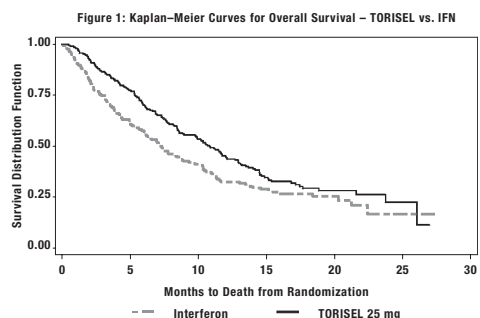
* A comparison is considered statistically significant if the p-value is <0.0159 (O'Brien-Fleming boundary at 446 deaths).

** Not adjusted for multiple comparisons.

^a Based on log-rank test stratified by prior nephrectomy and region.

^b Based on Cox proportional hazard model stratified by prior nephrectomy and region.

^c Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.



15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. NIH [2002]. 1999 recommendations for the safe handling of cytotoxic drugs. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 92-2621.
4. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.
5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0008-1179-01 TORISEL® (temsirolimus) injection, 25 mg/mL.
NDC 0008-1125-01 DILUENT for TORISEL®, 1.8 mL (deliverable volume) per vial.

These two vials are supplied as a kit in a single carton, and must be stored at 2°-8°C (36°-46°F). Protect from light.

U.S. Patent No. 5,362,718

17 PATIENT COUNSELING INFORMATION

- **Allergic (Hypersensitivity) Reactions**
Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis, despite premedication with antihistamines, and to immediately report any facial swelling or difficulty breathing [*see Warnings and Precautions (5.1)*].
- **Increased Blood Glucose Levels**
Patients are likely to experience increased blood glucose levels while taking TORISEL. This may result in the need for initiation of, or increase in the dose of, insulin and/or hypoglycemic agents. Patients should be directed to report any excessive thirst or frequency of urination to their physician [*see Warnings and Precautions (5.2)*].
- **Infections**
Patients should be informed that they may be more susceptible to infections while being treated with TORISEL [*see Warnings and Precautions (5.3)*].
- **Interstitial Lung Disease**
Patients should be warned of the possibility of developing interstitial lung disease, a chronic inflammation of the lungs, which may rarely result in death [*see Warnings and Precautions (5.4)*]. Patients should be directed to report promptly any new or worsening respiratory symptoms to their physician.
- **Increased Blood Triglycerides and/or Cholesterol**
Patients are likely to experience elevated triglycerides and/or cholesterol during TORISEL treatment. This may require initiation of, or increase in the dose of, lipid-lowering agents [*see Warnings and Precautions (5.5)*].
- **Bowel Perforation**
Patients should be warned of the possibility of bowel perforation. Patients should be directed to report

promptly any new or worsening abdominal pain or blood in their stools [*see Warnings and Precautions (5.6)*].

- **Renal Failure**
Patients should be informed of the risk of renal failure [*see Warnings and Precautions (5.7)*].
- **Wound Healing Complications**
Patients should be advised of the possibility of abnormal wound healing if they have surgery within a few weeks of initiating therapy or during therapy [*see Warnings and Precautions (5.8)*].
- **Intracerebral Bleeding**
Patients with CNS tumors and/or receiving anticoagulants should be informed of the increased risk of developing intracerebral bleeding (including fatal outcomes) while on TORISEL [*see Warnings and Precautions (5.9)*].
- **Medications that can interfere with TORISEL**
Some medicines can interfere with the breakdown or metabolism of TORISEL. In particular, patients should be directed to inform their physician if they are taking any of the following: Protease inhibitors, anti-epileptic medicines including carbamazepine, phenytoin, and barbiturates, St. John's Wort, rifampicin, rifabutin, nefazodone or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections [*see Warnings and Precautions (5.10)*].
- **Vaccinations**
Patients should be advised that vaccinations may be less effective while being treated with TORISEL. In addition, the use of live vaccines, and close contact with those who have received live vaccines, while on TORISEL should be avoided. [*see Warnings and Precautions (5.12)*].
- **Pregnancy**
TORISEL can cause fetal harm. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of TORISEL. [*see Warnings and Precautions (5.13)*].

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

Manufactured for: Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101

TORISEL® (temsirolimus) injection is manufactured by: Pierre Fabre Medicament Production, Aquitaine Pharm International, Avenue du Bearn, F64320 Idron, France

DILUENT for TORISEL® is manufactured by: Ben Venue Laboratories, Inc., Bedford, Ohio 44146-0568

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